Genetic Isolates in Human Populations. How and why studying them?
Identifying signatures of genetic isolation is more challenging in humans than in other animal species.
Genetic diversity at molecular level is smaller among humans than in other primates.
Understanding of the genetic structure of human populations;
Studies of human genetic isolates have proven to be extremely useful for mapping genes for rare monogenic disorders and complex diseases.
Genetic isolation in humans is often hypothesized to be associated with cultural diversity;
Very important in

- **Anthropology**: Peopling events, past migrations, demographic behavior, and cultural and linguistic features
- **Population Genetics**: Identifying the factors that account for genome variation (e.g., assortative mating, genetic drift, bottleneck effect)
- **Medical Genetics**: Monogenetic diseases, complex diseases
What is a genetic isolate?

Genetic isolates are subpopulations derived from a small number of founders that have been isolated, resulting from geographical and/or cultural barriers, for many generations with a very restricted genetic exchange with other subpopulations.
Characteristics of isolated population:

- limited number (10-100) of founders.
- Isolation because cultural or geographic barriers
- homogeneity of the shared environmental factors
- Access genealogical records
- reduced phenotypic and genetic heterogeneity
- limited number of recombination events in the DNA (increase LD)
Isolated populations, such as Finnish, Old Order Amish, Jewish, Sardinian, have proved to be invaluable resources for mapping genes involved in rare diseases that show a Mendelian recessive mode of inheritance.
The plant and animal biodiversity found on Italian territory is among the richest in the Mediterranean basin and in Europe as a whole.
Biodiversity in Italy

Tundra alpina

Zona arida mediterranea
Does the great variety observed in Italy for plants and animals hold for human populations?
Biodiversity in Italy

The European languages

INDOEUROPEAN LANGUAGES

ROMANCE LANGUAGES
- Aragonés (Aragonese)
- Asturianu (Asturian)
- Basque (Euskara)
- Catalan (Catalan)
- Coisq (Corsican)
- French (French)
- Galician (Galician)
- Italian (Italian)
- Occitan (Occitan)
- Portuguese (Portuguese)
- Romanian
- Sardinian (Sard)
- Walloon (including Picard, Lorrain, and Champenois)

SLAVIC LANGUAGES
- Belarusian
- Bulgarian
- Kashubian
- Croatian
- Czech
- Polish
- Pomeranian
- Russian
- Slovak
- Sorbian
- Ukrainian

BALTIC LANGUAGES
- Latvian
- Lithuanian

ALBANIAN LANGUAGE
- Albanian

GREEK LANGUAGE
- Greek (Greek)

TURKISH LANGUAGES
- Turkish

BASQUE LANGUAGE
- Euskara (Basque)

FINN-UGRIC LANGUAGES
- Estonian

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At present, 12 ethno-linguistic minorities are officially recognized and safeguarded by the Italian legislation: Albanian, Catalan, Croatian, French, Franco-provençal, Friulian, German, Greek, Ladin, Occitan, Slovene and Sardinian. Other minorities are recognized only by Regional legislation (Tabarkino, Veneto, Piemontese).
PROGETTI DI INTERESSE NAZIONALE (PRIN)

PRIN 2007
Isolating the isolates: analisi dei fattori geografici e culturali della variabilità genetica umana

PRIN 2009
La Biodiversità umana in Italia: patterns microevolutivi
Uniparental markers

Y Chromosome Y

mtDNA

Key: PAR: Pseudoautosomal region
SRY: Sex-determining region of the Y
MSY: Male-specific region of the Y
>Ind1
TATTGTACGGTACCATAAATACTTGACCACCTGTAAGTACATAAAAAACCCCAATCCACATCAAAACCCCCCT
CCCCATGCTTACAAGCAAGTACAGCAATCAACCCTCAACTATCACACTCAACTGC
Y-STRs
Comunità di minoranza
L. 482/99 e S.A. Prov. BZ/Sudtirolo
• Born and resident for at least 3 generations (grandparents rule)

• Founder surnames
57 populations

10 populations under geolinguistic isolation

16 populations under geographic isolation

3 populations under linguistic isolation

28 open populations
Comparing data

- Italian and European open population

Uniparental Markers in Italy Reveal a Sex-Biased Genetic Structure and Different Historical Strata
Alessio Boattini, Begona Martinez-Cruz, Stefania Sarno, Christine Harmant, Antonella Uselli, Paula Sanz, Daniele Yang-Yao, Jeremy Manry, Graziella Ciani, Donata Luisselli, Lluís Quintana-Murci, David Comas, Davide Pettener, the Genographic Consortium

Evidence of high genetic variation among linguistically diverse populations on a micro-geographic scale: a case study of the Italian Alps

Uniparental Markers of Contemporary Italian Population Reveals Details on Its Pre-Roman Heritage
Francesca Brisighelli, Vanesa Álvarez-Iglesias, Manuel Fondevila, Alejandro Blanco-Verea, Angel Carracedo, Vincenzo L. Pascali, Cristian Capelli, Antonio Salas

Paternal and maternal lineages in the Balkans show a homogeneous landscape over linguistic barriers, except for the isolated Aromuns
E. Bosch, F. Calafell, A. González-Neira, C. Flai, E. Mateu, H.-G. Scheil, W. Huckenbeck, L. Efremovska, I. Mikerezi, N. Xirotiris, C. Grasa, H. Schmidt and D. Comas

The population history of the Croatian linguistic minority of Molise (southern Italy): a maternal view
Carla Babalini, Cristina Martinez-Labarga, Helle-Vivi Tolk, Toomas Kivisild, Rita Giampaolo, Tiziana Tarsis, Irene Contini, Lovorka Barać, Branka Janićijević, Irena Martinović Klarić, Marijana Peričić, Anita Sujoldžić, Richard Villems, Gianfranco Biondi, Pavlo Rudan and Olga Rickards
Linguistic, geographic and genetic isolation: a collaborative study of Italian populations

Marco Capocasa²,³, Paolo Anagnostou¹,², Valeria Bachis⁴, Cinzia Battaggia¹, Stefania Bertoncini⁵, Gianfranco Biondi⁶, Alessio Boattini⁷, Ilaria Boschi⁸, Francesca Brisighelli¹,⁹, Carla Maria Calò⁴, Marilisa Carta⁷, Valentina Coia¹⁰,¹¹, Laura Corrias⁴, Federica Crivellaro¹², Sara De Fanti⁷ Valentina Dominici¹,², Gianmarco Ferri¹³, Paolo Francalacci¹⁴, Zelda Alice Franceschi¹⁵, Donata Luiselli⁷, Laura Morelli¹⁴, Giorgio Paoli⁵, Olga Rickards¹⁶, Renato Robledo¹⁷, Daria Sanna¹⁴, Emanuele Sanna⁴, Stefania Sarno⁷, Luca Sineo¹⁸, Luca Taglioli⁵, Giuseppe Tagarelli¹⁹, Sergio Tofanelli⁵, Giuseppe Vona⁴, Davide Pettener⁷ & Giovanni Destro Bisol¹,²
Linguistic, geographic and genetic isolation in Italian populations

Lower values of HD for isolated populations, particularly for Sappada, Ogliastra

Lower values of HD for isolated populations, particularly for Luserna, Timau and Sappada
Higher values of Fst for isolated populations, Particularly significative for Sappada, Vallepietra and Sauris

Higher values of Fst for isolated populations, Particularly for Luserna, Timau and Sappada
Italian isolates analysed through mtDNA
Italian isolates analysed through Y-STRs
AMOVA (within group) y

<table>
<thead>
<tr>
<th>Region</th>
<th>AMOVA (%)</th>
</tr>
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<tbody>
<tr>
<td>Italy without isolates</td>
<td>0.38%</td>
</tr>
<tr>
<td>Europe without isolates</td>
<td>0.33%</td>
</tr>
<tr>
<td>Italy with isolates</td>
<td>1.89%</td>
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<tr>
<td>Europe with isolates</td>
<td>1.52%</td>
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AMOVA (within group) mtDNA

<table>
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<tr>
<th>Region</th>
<th>AMOVA (%)</th>
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</thead>
<tbody>
<tr>
<td>Italy without isolates</td>
<td>3.19%</td>
</tr>
<tr>
<td>Europe without isolates</td>
<td>6.89%</td>
</tr>
<tr>
<td>Italy with isolates</td>
<td>8.95%</td>
</tr>
<tr>
<td>Europe with isolates</td>
<td>10.60%</td>
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</table>
### AMOVA (within group)

<table>
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<th>Group</th>
<th>Percentage</th>
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In Italy numerous populations with evident sign of genetic isolation are present.

These signs are more frequent in populations under geographic and linguistic isolation.

Strong genetic variability in Italy, greater than Europe, particularly for mtDNA.

Italian human genetic variability shows a pattern similar to what was observed for plants and mammals.
Case study: *The Arbereshe: between Italy and the Balkans*

One of the most numerous linguistic minorities in Italy
50 communities with around 100,000 individuals

**Arbereshe from Calabria**
30 communities with ~ 60,000 individuals

**Arbereshe from Sicily**
3 communities with ~ 15,000 individuals

Language: Arbereshe (albanian)
Religion: orthodox christian
Origin: south Albania (Toskeria)
Arrive in Italy: 1400-1500 A.D.
The Arbereshe are one of the largest linguistic minorities settled in Italy. They originated from migratory waves from Albania between the end of the 15th and beginning of the 16th century in response to the invasion of the Balkans by the Ottoman Empire.
Signes of isolation

Religion
Language
Surname analysis

Arbereshe populations are clearly distinguishable from their Italian neighbours. Arbereshe groups showed considerably higher marital isonymy levels than in Italians (0.080 vs 0.050). All these lines of evidence suggest that Arbereshe are a group of populations that have undergone cultural isolation.
Haplotype diversity

Calabrian Arbresh
Y chromosome: 0.976
mtDNA: 0.995

Sicilian Arbereshe
Y chromosome: 0.979
mtDNA: 0.992

very close to those of Italian neighbour populations of Cosenza (0.994 and 1.000) and Trapani-Enna (0.985 and 0.999).
Case study:

*The Arbereshe: between Italy and the Balkans*
Italian isolates: the case Sardinia
Sardinia: an outlier
Classical genetic markers: 40 alleles
(Piazza et al., 1988)

Dendrogram with 26 European populations
88 alleles
(Cavalli-Sforza et al., 1994)
Genetic tree build with 13 classical genetic markers (Memmì et al., 1998)
Original Research Article

β-Globin Cluster Haplotypes in Normal Individuals and β°39-Thalassemia Carriers From Sardinia, Italy


1st component 42.7%

2nd component 20.2%

Corsica, Sardinia, Lebanon, Cyprus, Sicily, Campania, Apulia, Spain, Portugal, Greece, Calabria, Po Delta, Sicily, Bulgaria.
Peopling of Three Mediterranean Islands (Corsica, Sardinia, and Sicily) Inferred by Y-Chromosome Biallelic Variability

P. Francalacci,¹,² L. Morelli,² P.A. Underhill,² A.S. Lillie,² G. Passarino,³ A. Useli,¹ R. Mokaddem,¹ G. Paoli,¹ S. Tozanelli,² C.M. Caba,³ M.E. Ghiani,³ L. Varesi,³ M. Memini,³ G. Vona,³ A.A. Lin,³

Sardinia

France

Corsica

Catalonia

N-C Italy

Greece

Sicily

Calabria
Distribution of M26 mutation in Y chromosome (aplotgroup I2a)
Percentage of Y haplogroups considered of Neolithic and Paleolithic origin

- Neolithic: 35%
- Paleolithic: 61%
- Others: 4%
Linguistic areas

- Sassarese
- Gallurese
- Nord-ovest Logudoro
- Est Logudoro
- Sud Logudoro – Planargia
- Goceano (alta valle del Tirso)
- Circondario di Bitti
- Nuorese
- Baronia di Orosei-Siniscola
- Monti Ferru
- Fonni – Barbagia di Ollolai
- Nord Campidano di Oristano
- Media valle del Tirso
- Barbagia di Belvi
- Ogliastra
- Sud Campidano di Oristano
- Tregenta – Parteolla
- Transizione tra Gerrei e Tregenta
- Sarrabus
- Sulcis – Iglesiente
- Campidano di Cagliari
- Alghero
- Carloforte
Genetic structure:
Internal diversity

Genetic boundaries obtained using 12 classical genetic markers
L’Ogliastra
Genome-wide scan with nearly 700,000 SNPs in two Sardinian sub-populations suggests some regions as candidate targets for positive selection

In black
Ogliastro,

In red
Trexenta and
Sulcis
High Differentiation among Eight Villages in a Secluded Area of Sardinia Revealed by Genome-Wide High Density SNPs Analysis

Giorgio Piscitelli, Ignazio Piccialli, Nicola Picciolo, Ivana Petrucci, Alessandro Sassu, Andrea Piscitelli, Domenico Prodol, Cristina Feaumeone, Evelina Morici, Maria Teresa Maina, Rostano Atzeni, Massimiliano Cossu, Mario Pizzuti, Andrea Angius.
Isolates in Sardinia

Carloforte: Geo/linguistic isolate

Benetutti: geographic isolation
Both the isolates show a decrease of internal variability both for mtDNA and Ychromosome.

Probable different admixture: males from Carloforte with females from Tunisia.
Desulo

2435 abitanti
Isolates in Sardinia
Isolates in Sardinia
Analysis of a Genetic Isolate: The Case of Carloforte (Italy)

R. Robledo, L. Corrias, V. Bachis, N. Puddu, A. Mameli, G. Vona, and C. M. Calò

Human Biology, December 2012, v. 84, no. 6, pp. 735-754.
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Case study: Carloforte
History of Carloforte

![Map of Carloforte and surrounding areas with key events: Genova/Pegli in 1542 and Tabarka in 1738.](image)
Tabarchino, which is part of the Ligurian group of Romance dialects.
Matrimonial behaviour: endogamy, consanguinity
Surnames analysis
Surnames analysis
Genetic analysis: classical markers

(Vona et al., 1996)
Genetic analysis:
Y-chromosome haplogroups
Founder-surnames sampling is not affected by recent gene flow and is therefore a signature of the ancestral population, whereas the grandparents’ criterion is a signature of the present population.
In Carloforte: frequent a genetic form of high myopia, very rare in the rest of the island, but it presents the lowest frequency (0.5‰) of Multiple sclerosis in Sardinia, while Sulcis (the region nearest to Carloforte) present the highest incidence in Sardinia (2‰).
Lingua diversa = diversità genetica?

Alghero
Only a multidisciplinary approach allows the knowledge of all those parameters, which is essential to understand the present genetic structure of the population.
Multidisciplinary approach in determining the features of a genetic isolate.